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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/827,493 | 04/06/2001 | Lenard M. Lichtenberger | 96606/15UTL | 5746 |

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| EXAMINER |
|---|
| JIANG, SHAOJIA A |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

DATE MAILED: 05/07/2003

18

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/827,493 | LICHTENBERGER, LENARD M. | |
| | Examiner | Art Unit | |
| | Shaojia A. Jiang | 1617 | |

*-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *33-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 13, 2003 has been entered in Paper No. 16.

This Office Action is a response to Applicant's request for continued examination (RCE) filed February 13, 2003 in Paper No. 16, and response to the Final Office Action (mailed November 13, 2002), filed February 13, 2003 in Paper No. 17. Currently, claims 1-45 are pending in this application.

Claims 33-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention (see the previous Office Actions November 13, 2002 and February 12, 2002).

Claims 1-32 are examined on the merits herein.

Applicant's declaration of Dr. Lenard M. Lichtenberger (inventor) submitted February 13, 2003 in Paper No. 17 under 37 CFR 1.132, is acknowledged and will be further discussed below.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over DAIFOTIS, et al. (WO 9904773, of record) in view of Lichtenberger et al. (5,763,422, of record), further in view of Hovancik et al. (5,869,471, of record).

Daifotis et al. discloses that bisphosphonates such as alendronate, risedronate, tiludronate and ibandronate, within the instant claims, are known to be useful in pharmaceutical compositions and methods for treating osteoporosis. See abstract, page 1 lines 14-15 and page 2 lines 1-15. Daifotis et al. also discloses that bisphosphonates are known to have low bioavailability from GI tract and therefore cause adverse GI effects. See abstract, page 1-3. Further, Daifotis et al. discloses that the purpose of the methods therein are for inhibiting bone resorption in mammals to treat osteoporosis while minimizing the adverse GI effects (see abstract and page 7 lines 22-23 in particular). Daifotis et al. also discloses the effective amounts of bisphosphonates to be administered in the compositions therein for minimizing the adverse GI effects (see Examples at page 24-27)

Daifotis et al. do not expressly disclose the employment of one zwitterionic phospholipid to reduce GI toxicity of bisphosphonate when administering at least one bisphosphonate in a pharmaceutical composition. The prior art does also not expressly disclose the effective amounts of active agents in the composition herein to be administered.

Lichtenberger et al. disclose that zwitterionic phospholipids, within the instant claims, (see abstract, col.3 lines 59-67, col.10 lines 50-62, col.11 lines 60-65) are capable of reducing GI irritating (adverse) effects and is therefore useful broadly in combining with many NSAID drugs (see Table I at col.4 lines 25-52) in pharmaceutical compositions since NSAID drugs may cause GI adverse effects, e.g., inducing GI ulcers and bleeding. See also abstract and col.1-2. Lichtenberger et al. also disclose the effective amounts of zwitterionic phospholipids in the pharmaceutical compositions therein. See col.12 lines 12-34.

Hovancik et al. discloses that the combination of NSAIDs and bisphosphonates is useful in improving the therapeutic effect for treating arthritis (bone disorders) (see col. 1-3, especially col.3 lines 3-7).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine one zwitterionic phospholipid to reduce GI toxicity of bisphosphonate when administering at least one bisphosphonate in a pharmaceutical composition, and to optimize the effective amounts of active agents in the composition herein to be administered.

One having ordinary skill in the art at the time the invention was made would have been motivated to combine one zwitterionic phospholipid to reduce GI toxicity of bisphosphonate when administering at least one bisphosphonate in a pharmaceutical composition since zwitterionic phospholipids are known to be capable of reducing GI irritating (adverse) effects that caused by other drugs such as many NSAIDs according to Lichtenberger et al. Moreover, bisphosphonates such as alendronate, risedronate,

tiludronate and ibandronate are known to cause adverse GI effects and the purpose of the method of Daifotis et al. is known to minimize the adverse GI effects induced by bisphosphonates. Further, the combination of NSAIDs and bisphosphonates is known to be useful in methods for treating bone disorders, and the combination of NSAIDs and zwitterionic phospholipids is also known to be useful in methods for treating bone disorders.

Therefore, one of ordinary skill in the art would have reasonably expected that combining one zwitterionic phospholipid and a bisphosphonate in a composition to be administered would reduce or minimize adverse GI effects induced by the bisphosphonate. Hence, the combined teachings of Daifotis and Lichtenberger Hovancik have provided the motivation of the instant invention.

Additionally, one of ordinary skill in the art would have been motivated to optimize the effective amounts or ratio of zwitterionic phospholipid and a bisphosphonate in a composition because the effective amounts of zwitterionic phospholipid to be administered are known in the art. Moreover, the optimization of amounts of active agents to be administered is considered well within the skill of artisan, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant's remarks and the declaration of Dr. Lenard M. Lichtenberger (inventor) submitted February 13, 2003 in Paper No. 17 under 37 CFR 1.132 with respect to this rejection of claims 1-32 made under 35 U.S.C. 103(a), of record stated in the Office Action dated November 13 , 2002 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art for the following reasons.

Again, Applicant arguments that there is no motivation to combine because there is no reasonable expectation that their combination would be successful are not found persuasive. As Applicant admits, Daifotis et al. clearly teaches that bisphosphonates can cause adverse GI effects when ingested. Daifotis et al. also disclose that their invention relates to methods for inhibiting bone resorption in mammals to treat osteoporosis while minimizing the occurrence of or potential for adverse GI effects (see page 1 lines 11-13). Thus, the teachings of Daifotis et al. are seen to provide the motivation to make the present invention in reducing GI toxicity induced by bisphosphonates.

Moreover, zwitterionic phospholipids (within the instant claims) are known to be capable of reducing GI irritating (adverse) effects and are therefore useful broadly in combining with NSAID drugs in pharmaceutical compositions in order to reduce GI adverse effects, e.g., inducing GI ulcers and bleeding, caused by NSAID drugs, according to Lichtenberger et al. As discussed in the previous Office Action, one of ordinary skill in the art, therefore, would have reasonably expected that combining one zwitterionic phospholipid and a bisphosphonate in a composition to be administered

would reduce or minimize adverse GI effects induced by the bisphosphonate with reasonable expectation for success, absent evidence to the contrary.

Additionally, Hovancik et al. has been cited by the examiner primarily for its teachings of that the combination of NSAIDs and bisphosphonates is useful in improving the therapeutic effect for treating arthritis (bone disorders) (see col. 1-3, especially col.3 lines 3-7), further supports the examiner's position, since that the combination of NSAIDs and bisphosphonates is known to be useful in methods for treating bone disorders, and the combination of NSAIDs and zwitterionic phospholipids is also known to be useful in methods for treating bone disorders. Thus, one of ordinary skill in the art would reasonably expect that the combination of bisphosphonates and zwitterionic phospholipids would be successful in treating bone disorders, the same disorders, absent evidence to the contrary.

Applicant's arguments regarding that "the motivation to combine these to references is derived exclusively from hindsight" have been considered but are not found persuasive. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971). See MPEP 2145.

Therefore, as discussed above, motivation to combine the teachings of the prior art to make the present invention is seen and no improper hindsight is seen. The claimed invention is clearly obvious in view of the prior art.

Dr. Lichtenberger's declaration herein is ineffective to overcome the 103(a) rejection herein since it is not seen to provide clear and convincing evidence of nonobviousness or unexpected results for the combination herein over the prior art. The declaration merely presents the testing results of the reduction of hydrophobicity of DPPC monolayers on glass slides with two particular bisphosphonates, which is not seen to be factual data for unexpected results the claimed combination herein in reducing GI toxicity caused by bisphosphonates because no testing results in *vivo* and no zwitterionic phospholipids employed in the testing are presented.

Therefore, the declaration is insufficient to rebut the prima facie case herein.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (703) 305-1008. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (703) 305-1877.

The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
April 28, 2003

SREENI PADMANABHAN
PRIMARY EXAMINER
(SPE) 1617